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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,139	08/08/2001	Rosanne M. Crooke	ISPH-0596	3066

36441 7590 03/16/2004

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,139	CROOKE ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,12,13,15 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,12,13,15 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Previously Indicated Allowable Subject Matter

1. The indicated allowability of claims 4-10 and 12-15 is withdrawn in view of the rejection set forth below.

Status of Application/Amendment/Claims

2. Applicant's response filed December 29, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed October 7, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

4. Claims 4-10, 12, 13, 15, and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., in view of Drayna et al., Taylor et al. (Taylor is newly of record), Baracchini et al., and Bennett et al.

The invention of the above claims is drawn to antisense compounds, their internucleoside, sugar, nucleobase, and 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents or colloidal dispersion systems thereof

that target nucleobases 1631 to 1769 of human cholesteryl ester transfer protein of SEQ ID NO: 3 and inhibit its expression.

Liu et al. teach an antisense compound with phosphorothioate modifications that targets and inhibits the expression of the same gene targeted by applicants, that is, human cholesteryl ester transfer protein. Liu also teaches such compounds in pharmaceutically acceptable diluents, but does not teach said compound targeting the specific region of nucleobases 1631 to 1769 of human cholesteryl ester transfer protein. Liu et al. does not teach such compounds that comprise sugar, nucleobase, and 2' modifications, and chimeras.

Drayna et al., teach the cDNA sequence encoding human cholesteryl ester transfer protein of SEQ ID NO: 3, identical to applicants' claimed target.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teach modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to achieve gene inhibition.

Bennett et al. teach how to inhibit specific mRNA transcripts using antisense compounds that target the 5'-untranslated region, the start codon region, the stop codon region, or the 3'-untranslated region of said transcript, and also teach modifications of antisense compounds

comprising the specific sugar, nucleobase, 2' modifications, chimeras, and pharmaceutical preparations currently claimed by applicants.

It would have been obvious to make modified antisense oligos targeted to applicants instant SEQ ID NO: 3 as taught by Liu et al. It also would have been obvious to target antisense oligonucleotides targeted to the region 1631 through 1769 of the sequence of human cholesteryl ester transfer protein as taught by Drayna et al., (this region corresponds to essentially the entire 3' untranslated region, see applicants table 1). It also would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by both Baracchini et al. and Bennett et al. into such antisense compounds.

One of ordinary skill would have been motivated to make and use antisense oligos to inhibit the instant target of SEQ ID NO: 3, because Liu expressly teach modified antisense oligos targeted to applicants instantly claimed target of SEQ ID NO: 3. (taught by Drayna et al.). Further motivation to inhibit this target comes from Liu et al., who teaches that inhibiting human cholesteryl ester transfer protein may counteract atherosclerosis, and also because Drayna et al. teach that said protein plays an important role in pathological cholesterol homeostasis. Therefore, one would have been motivated to make such modified compounds targeted to the inhibition of applicants SEQ ID NO: 3 to investigate its role in atherosclerosis and related pathologies.

One would have been motivated to target the 3'UTR (the region of SEQ ID NO: 3 bounded by nucleotides 1631 to 1769) as claimed by applicants because both Baracchini et al. and Bennett et al. teach that this region is known in the art as a preferred target region. Furthermore, one would have been motivated to modify such antisense compounds to make them more resistant to degradation, because Liu et al. expressly teach modified oligos resistant to

degradation, and because both Baracchini et al. and Bennett et al. teach all the modifications instantly claimed by applicants, and also teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

Finally, one would have a reasonable expectation of success given that successful antisense-mediated inhibition of human cholesteryl ester transfer protein using modified oligos was previously demonstrated by Liu et al. Furthermore, the steps involved in making such modified oligos targeted to a gene are disclosed in a highly detailed manner by both Baracchini et al. and Bennett et al., including starting reagents, synthesis protocols, equipment manufacturers, and precise assays for determining the effectiveness of the oligos administered. Finally, one would have a reasonable expectation of success in finding such inhibitory oligos given that Taylor et al. teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. and Bennett et al. teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD

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James Douglas Schultz, PhD

SEAN McGARRY
PRIMARY EXAMINER
1635